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# Effectiveness of mirtazapine in the treatment of depression with associated somatic symptoms

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**Introduction.** To assess the efficacy of mirtazapine in the treatment of depression with somatic symptoms in a 3-months follow-up study.

**Material and methods.** Design: multicenter, prospective, observational, open-label, and non controlled study. Sample: seven hundred and eleven patients recruited in outpatient psychiatric consultations by 98 psychiatrists nationwide. Instruments: 17-Item Hamilton Depression Rating Scale (HAMD-17) and Standardized Polyvalent Psychiatric Interview (SPPI), somatic symptoms section. Patients were assessed pretreatment and at 15, 30 and 90 days post-treatment.

**Results.** Severity of depression assessed by HAMD-17 significantly decreased ( $p < 0.0001$ ) from 23.27 in the pretreatment assessment to 6.75 at 3 months post-treatment. Severity of somatic symptoms assessed by EPEP significantly decreased ( $p < 0.0001$ ) from 7.68 in the pre-treatment assessment to 2.28 at 3 months post-treatment. Mirtazapine modifies attribution of somatic symptoms in somatizers: in pretreatment assessment, 41.3% of the sample attributed somatic symptoms to a psychological origin, while at 3 months post-treatment this percentage significantly increased ( $p < 0.05$ ) to 63.94%. Nearly half of the sample (48.52%) took benzodiazepines at the start of the study; but at 3 months post-treatment only 6.71% of the patients needed them. The incidence of adverse effects was 13.36% of the patients. From the total dropouts 4% were due to adverse events.

**Conclusions.** Mirtazapine is an effective and safe antidepressant for the treatment of depression with somatic symptoms and is able to modify attribution of somatic symptoms in somatizing patients.

**Key words:**

Mirtazapine. Depression. Attribution. Somatic symptoms. Treatment.

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## Effectiveness of mirtazapine in the treatment of depression with associated somatic symptoms

**Introducción.** Se evalúa la evolución clínica de la depresión con síntomas somáticos durante los primeros 3 meses de tratamiento con mirtazapina.

**Material y métodos.** Diseño: estudio multicéntrico, prospectivo, observacional, abierto y no controlado. Muestra: 711 pacientes seleccionados por 98 psiquiatras de todo el territorio español que trabajaban en consultas externas de psiquiatría. Instrumentos: se utilizó la Escala de Depresión de Hamilton de 17 ítems (HAMD-17) y la Entrevista Psiquiátrica Estandarizada Polivalente (EPEP), sección síntomas somáticos. Los pacientes fueron evaluados pretratamiento y a los 15, a los 30 y a los 90 días post-tratamiento.

**Resultados.** La intensidad de la depresión medida con la HAMD-17 disminuye significativamente ( $p < 0,0001$ ) desde 23,27 pretratamiento hasta 6,75 a los 3 meses. La intensidad de la sintomatología somática medida con la EPEP disminuye significativamente ( $p < 0,0001$ ) desde 7,68 pretratamiento hasta 2,28 a los 3 meses. Mirtazapina modifica la atribución de los síntomas somáticos en somatizadores: en la visita basal el 41,37% de la muestra pensaba que la causa de los síntomas era psicológica, mientras que a los 3 meses el porcentaje se había incrementado significativamente ( $p < 0,05$ ) a un 63,94%. La mitad de la muestra (48,52%) tomaba benzodiazepinas al inicio del estudio; mientras que tras 90 días de tratamiento, sólo precisaron asociar benzodiazepinas un 6,71% de los pacientes. La incidencia de efectos adversos fue del 13,36% de los pacientes. Del total de los abandonos del estudio, solamente un 4% fueron debidos a acontecimientos adversos.

**Conclusiones.** Mirtazapina es un antidepresivo eficaz y seguro para el tratamiento de los pacientes depresivos con síntomas somáticos asociados y es capaz de modificar la atribución de los síntomas en pacientes somatizadores.

**Palabras clave:**

Mirtazapina. Depresión. Atribución. Síntomas somáticos. Tratamiento.

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## INTRODUCTION

Depression is a serious disease and is considered to be a relevant problem in public health<sup>1</sup>. Prevalence indexes between 4.4% and 19.6% have been described for major depression and between 3.1% and 3.9% in dysthymia<sup>2</sup>. Depression entails an elevated economic cost. This is not only in regards to direct costs (costs related with care for hospitalized and out-patients, treatment, days of hospitalization, etc.) but also indirect costs such as loss of hours worked, payment of pensions, work absenteeism, etc. The direct costs of depression represent a greater financial burden than chronic diseases such as asthma, diabetes or schizophrenia<sup>3</sup>.

Depression with somatic symptoms is considered to be an important subtype of depression. Some of the first studies that approached this subject, such as that of Hamilton<sup>4</sup>, documented an 80% prevalence of somatic symptoms in depressive patients. From a biomedical perspective, it was thought that there were physical symptoms specifically associated to depression, such as fatigue, weakness and pain<sup>5</sup> that formed an integral part of the depressive syndrome and that reflected subjacent neurobiological abnormalities<sup>6</sup>. On the contrary, another group of symptoms such as palpitations, dyspnea or paresthesias are considered to be intrinsically related with anxiety disorders<sup>7</sup>.

In recent years, the WHO has conducted a series of studies on somatization worldwide<sup>8,9</sup> that may be considered definitive on the subject due to the size of the sample (N=5,438 patients) and the extensive international representativity as the sample was obtained in 15 different countries and with careful methodology. Said studies have concluded that: *a)* depression occurs systematically with somatic symptoms; *b)* there are no somatic symptoms specifically associated to anxiety or depression, and *c)* the somatization is distributed similarly by all the countries with scarce differences and independently of the type of culture and grade of socioeconomic development. The studies conducted in Spain<sup>10</sup> show that more than 10% of the primary care patients have depression and that these depressions are associated to somatic symptoms in most of the cases.

The efficacy of the antidepressive drugs is well-established in the treatment of depression<sup>11</sup>. Both neurobiological and neuroanatomical research provides evidence that shows the importance of the modifications of the noradrenergic and serotonergic systems in the success of antidepressive treatment<sup>12</sup>. Mirtazapine has a dual action mechanism that is different from the remaining antidepressants currently used. It increases noradrenergic and serotonergic neurotransmission through the blockage of the central autoreceptors and  $\alpha_2$  heteroreceptors. The increased release of serotonin mediated by serotonergic neuron stimulation will only stimulate the 5-HT<sub>1</sub> receptors, since the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> are specifically blocked by mirtazapine<sup>13</sup>. Thus, mirtazapine may be described as a NaSSA, or «Noradrenergic and

Specific Serotonergic Antidepressant». The increase of the neurotransmission by both noradrenergic and serotonergic systems, specifically through the 5-HT<sub>1</sub> receptors, is considered to be responsible for the global antidepressive activity of mirtazapine<sup>14,15</sup>.

Pain is the symptom that patients with depression have most frequently<sup>6</sup>. The results of the study of the Onghena and Van Houdenhove meta-analysis<sup>16</sup> on the use of antidepressants with analgesic effect show that the most effective antidepressants are those that simultaneously act on serotonin and norepinephrine. Thus, mirtazapine would be especially indicated in these patients. The populational samples that participate in clinical studies are highly selected by a series of inclusion and exclusion criteria which, although they provide great internal validity to the studies, generally are somewhat distant from the characteristics of the real population of patients that are aimed at by a drug in the clinical practice. That is why the prospective naturalistic studies are being progressively introduced, because they collect what is really occurring in the clinical practice, far from the asepsis and bias of the research.

The purpose of this study is to evaluate the efficacy of mirtazapine in the treatment of depression with somatic symptoms in a large sample of psychiatric out-patients and the tolerance of the drug in this group of patients.

## MATERIAL AND METHODS

### Study design

Multicenter, prospective, observational and open label study with a 15, 30 and 90 day follow-up in patients diagnosed of depressive disorder with associated somatic symptoms who come to the mental health care centers (fig.1).

### Sample size

A total of 98 psychiatric investigators participated and valid information was obtained in 711 patients.

### Evaluation measurements

#### *17-item Hamilton Depression Rating Scale (HAMD-17)*<sup>17</sup>

17-item questionnaire that evaluates the severity of the depressive picture. The total score ranges from 0 to 52 points. It makes it possible to quantify the intensity of the depressive symptoms in patients diagnosed of depression. Those patients who are successful in decreasing their baseline symptoms by at least 50% are considered to be responders to treatment.

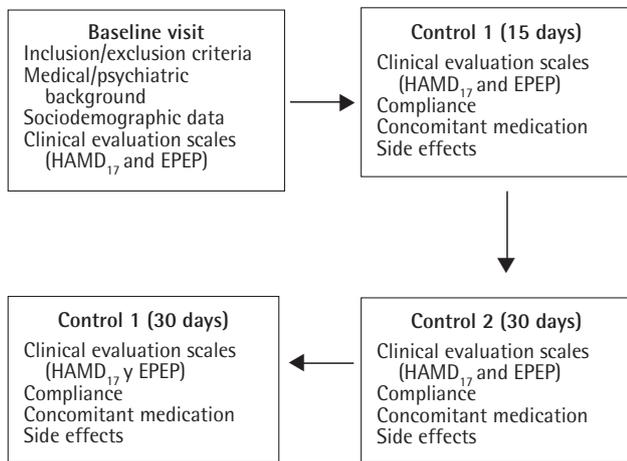


Figure 1 Study design.

*Standardized Polyvalent Psychiatric Interview (SPPI), somatic symptoms section<sup>18</sup>*

This is an assessment scale of the somatic symptoms in depression. It is made up of 4 sections with an independent assessment scale for each one of them, since they evaluate different features. The first section evaluates the number of somatic symptoms and their distribution. Each symptom that is present corresponds to one point and the maximum score that can be reached is 24. Evaluation of this section is made with a three-level scale that classifies the patients in the following groups: 0-3: mild somatic symptoms; 4-9: moderate somatic symptoms, and  $\geq 10$ : severe somatic symptoms.

The second section evaluates the intensity of the somatic symptoms on a scale of 0 (absent) to 4 (severe). The third section measures the incapacity that the symptoms cause, also on a scale of 0 (absent) to 4 (severe). Finally, the fourth section evaluates the attribution of the symptoms by the patient on a score that ranges from 0 (psychological attribution) to 2 (physical attribution).

**Incidence and characteristics of the adverse events**

The study was conducted in such a way as to make it possible to detect and record any adverse event in the participants. Adverse events were defined as:

- Any new sign or symptom that has appeared during the study period.
- Any preexisting sign or symptom at the onset of the study, but that increased in severity or frequency during the study period.

**Inclusion and exclusion criteria**

*Inclusion criteria*

As this was an observational study, the inclusion criteria were defined by the authorized indication of the drug:

- Age equal to or greater than 18 years.
- Patients with depressive disorder, according to the DSM-IV criteria for major depressive episode (categories 289.2 and 296.3), whether mild, moderate or significant.
- Baseline scores on the HAMD-17 scale of at least 8 points. This cutoff is lower than the usual 17 points used in the studies on depression. The reason for this is that the diagnosis had already been made clinically and it is demonstrated that the depression levels in somatizers are lower than in the psychologists<sup>19</sup>.
- Baseline scores in the symptoms section of the SPPI18: question 1: at least 4 points and/or question 2: at least 2 points.

*Exclusion criteria*

Exclusion criteria were fundamentally those characteristic of the drug data sheet. Patients who had any of the following conditions were not included:

- Concomitant presence of another psychiatric disorder as primary diagnosis or as priority reason for the treatment.
- Patients under treatment with MAOIs. At least 2 weeks must have passed since the MAOI treatment was discontinued for the onset of treatment with mirtazapine.
- Severe organic, incapacitating diseases or those with vital risk.
- Pregnancy or breast-feeding.
- Known hypersensitivity to the active ingredient or non-active ingredients.
- Participation of the patient in another study.

**Ethical aspects**

The study described in this protocol has been conducted in accordance with the version in force of the Declaration of Helsinki and subsequent ones and with the Spanish legislation on material of post-authorization pharmacovigilance of the drug. When studies of this type were conducted, approval of the Ethics Committee was not required. However, the patients signed an informed consent agreeing to participate in the study.

## Statistical analysis

A descriptive statistics was made initially. For the inferential statistics, parametric or non-parametric tests were used depending on the type of variable studied. Significance level was established at 0.05 as usual. The SPSS 11 program was used for the statistical program.

## RESULTS

### Sociodemographic and clinical characteristics of the sample

Mean age of the sample was 48.09 years ( $SD \pm 15.06$ ). Distribution by gender of the sample was 460 women (66%) and 236 men (34%), which implies a woman/man ratio of 1.94:1. Regarding civil status, most of the patients were married (61.3%), followed by single (19.2%) and separated/divorced (10.7%). Regarding work status, most were active (40.4%), with a significant percentage being housewives (26%) and retired (17.7%).

Regarding medical background, 33.1% of the patients had previous suffered or were presently suffering some concomitant organic disease at the time of the interview. According to systems, out of all the individuals who had organic comorbidity, 22.5% suffered musculoskeletal disorders, 14.9% cardiovascular, 11.5% gastrointestinal and 8.5% endocrine ones. In regards to psychiatric background, 27% of the total sample were suffering them. Of these, the most frequent were depressive disorder background (53% of the sample), followed by anxiety background (51%) and adaptive disorders (18%).

Focusing on the characteristics of the depressive episode, the duration of the depression was acute (<2 months) in 22% of the cases, subacute (2-6 months) in 48%, chronic (more than 6 months) in 15% and very chronic (more than 1 year) in 15%. Regarding intensity, 46% of the study sample had moderate depression according to the HAMD-17 criteria, 14% mild and only 40% of the participants had severe depression. Regarding the dose of mirtazapine used, 30 mg/day of mirtazapine were prescribed to the patients from the onset of the study, with dose adjustment at each visit based on the patient's clinical course. The medication was administered orally in a single night-time dose as 30 mg scored tablets. Mean dose of mirtazapine taken by the patients was 0.80 tablets of 30 mg/day for the first two weeks, 0.74 tablets during weeks 3 and 4 and 0.76 tablets per day during the second and third months

### Antidepressive efficacy

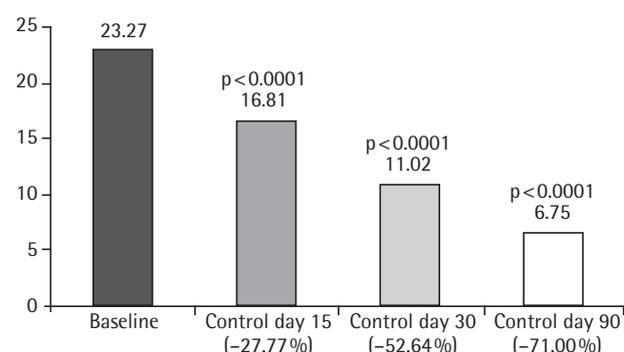
In order to illustrate the possible differences of the depressive symptoms from the onset of the treatment, Table I shows the evolution of the mean scores, item by item, from their baseline value and in each one of the successive visits (table 1).

Table 1		Summary of mean score evolution of each item of the Hamilton scale for depression during the study			
Ítem	Baseline	15 days	30 days	90 days	
Depressed mood	2.48	1.91	1.28	0.64	
Feeling of guilt	1.36	1.06	0.61	0.28	
Suicidal intention	1.07	0.70	0.33	0.09	
Early insomnia	1.51	0.80	0.43	0.29	
Middle insomnia	1.11	0.66	0.39	0.25	
Middle insomnia	1.04	0.66	0.41	0.26	
Work	2.36	1.98	1.42	0.85	
Inhibition	1.04	0.82	0.52	0.31	
Agitation	1.03	0.72	0.45	0.24	
Psychic anxiety	2.11	1.48	1.06	0.76	
Somatic anxiety	2.14	1.60	1.16	0.82	
Somatic sympt.- GI	1.19	0.82	0.49	0.28	
Somatic sympt general	1.40	1.11	0.84	0.62	
Genital symptoms	0.97	0.85	0.65	0.49	
Hypochondria	1.34	1.01	0.67	0.46	
Awareness of disease	0.42	0.30	0.17	0.09	
Weight loss	0.74	0.37	0.15	0.04	
Total	23.27	16.81	11.02	6.75	

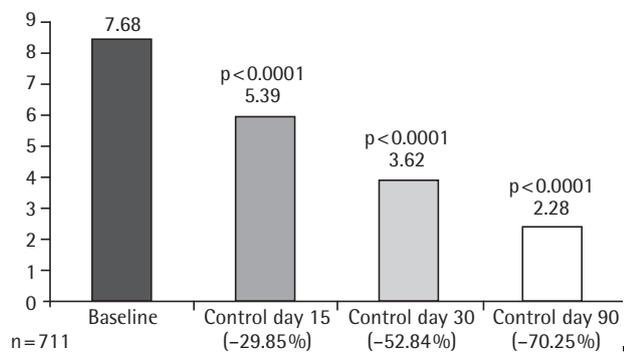
GI: gastrointestinal.

In figure 2, it can be seen that the mean score at the onset of the study on the Hamilton Depression scale was 23.27 ( $SD \pm 5.42$ ), while the mean score in the last control was 6.75 ( $SD \pm 4.44$ ), located within the so-called «non-depression». In regards to the evolution of each one of the items of the scale comparing each visit regarding the baseline value, it was observed that for each one of them, reduction of the score was already statistically significant ( $p < 0.0001$ ) from the first control (fig. 2).

If the course of the depressive symptoms of the patients is analyzed, we observe that 47% of the sample at the beginning



**Figure 2** Evolution of Hamilton Depression Scale during the study.



**Figure 3** Evolution of number of somatic symptoms.

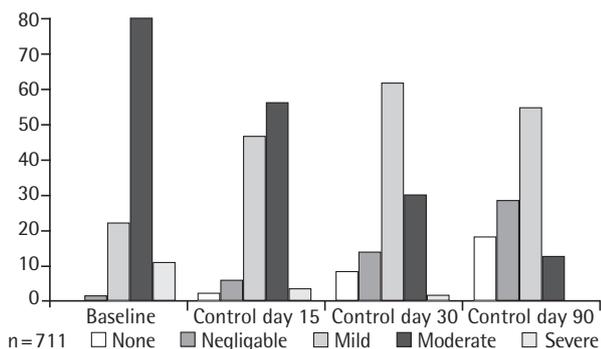
of the study had moderate depression and 40% significant depression. After 12 weeks of treatment with mirtazapine, only 3% of the patients had moderate depression and none had significant depression. The results of the study show that the depressive symptoms totally subsided in 61% of the sample.

The analysis of the evolution of the percentage of patients with good response, that is, with a decrease of 50% of their symptoms regarding the baseline value, shows that the percentage of responders to treatment in the second week was already 52.82% and 84.57% at 90 days.

### Efficacy in the treatment of associated somatic symptoms

In figure 3, it can be observed that the mean score in the first section of the SPPI, total number of somatic symptoms, was 7.68 (SD ± 3.13) at the onset of the study and 2.28 (SD ± 1.93) in the last control. The differences in all the controls were statistically significant (p < 0.0001) (fig. 3).

Figure 4 shows the mean score in symptom intensity. At the onset of the study, mean score was 2.85 that corresponds to moderate intensity. At the end of the study, mean



**Figure 4** Intensity of the symptoms.

score decreased to 1.47, equivalent to a negligible/mild intensity. The differences in all the controls were statistically significant (p < 0.0001) (fig. 4).

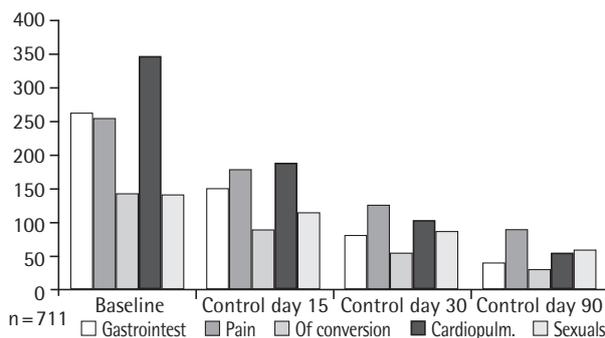
In the baseline control (fig. 5), the group of somatic symptoms having the greatest mean score is cardiopulmonary followed by gastrointestinal and pain. Temporal evolution of the groups of somatic symptoms shows a clear improvement during the study, this being statistically significant in all the controls (fig. 5).

If we analyze the group with cardiopulmonary symptoms, we verify that palpitations make up the symptom that appears most frequently in the baseline control, followed by breathing difficulty and dizziness. Abdominal pain is the gastrointestinal symptom that appears most frequently in the baseline control, followed by nausea and excessive intestinal gases. Regarding the group of symptoms related with pain during the study, we verified that the symptoms that appear with the greatest frequency in the baseline control are back pain followed by pain in the limbs and joints.

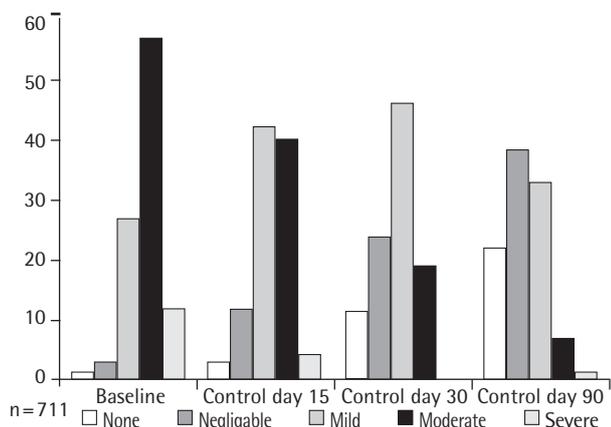
Involvement of family and professional life measured by SPPI can be seen in figure 6. At the onset of the study, the mean score was 2.73 that corresponds to moderate involvement of family or professional life and this decreased to 1.19 at the end of the study, equivalent to negligible/mild involvement. The differences in all the controls were statistically significant (p < 0.0001).

### Efficacy on the attribution of the somatic symptoms

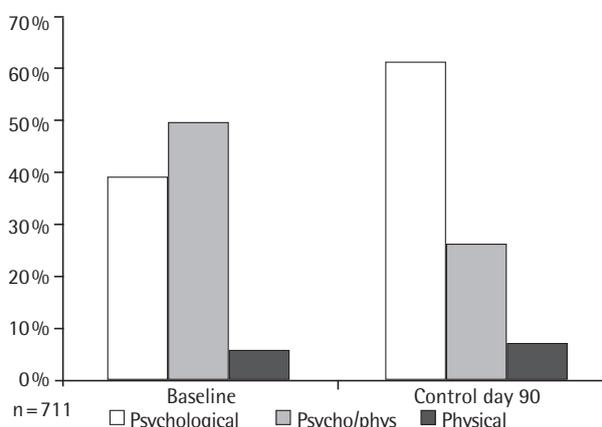
In figure 7, we observed that there is a significant temporal evolution in the percentage of individuals who attribute their semantic symptoms to a psychological disorder exclusively. In the baseline control, 41.37% of the patients attributed their symptoms to a psychological cause, this percentage increasing in the last control to 63.94% of the sample.



**Figure 5** Evolution of the intensity of the different groups of somatic symptoms of the SPPI.



**Figure 6** | *Involvement of family and professional life with SPPI.*



**Figure 7** | *Attribution of the somatic symptoms.*

### Termination of the study

Out of the 711 patients who initiated the study, 511 patients (77.49%) satisfactorily completed it. Only 4% of the dropouts were due to adverse effects (table 2), 5% were due to non-adherence to treatment and 14% more for other causes (losses to follow up, remissions, voluntary causes, etc.).

### DISCUSSION

Although it has been seen that Mirtazapine is effective in depression<sup>15</sup>, the purpose of this study consisted in evaluating the efficacy of it in depression with associated somatic symptoms under real clinical conditions. A total of

98 psychiatrists obtained valid information on 711 patients within the framework of an observational, open label and multicenter study. Thus, this is the largest study conducted nationally on drug treatment of depression with associated somatic symptoms. On the other hand, this study has important limitations associated to an open label and non-controlled study, the main one being that it was not possible to draw the boundaries of the impact of other variables on the final results such as the use of concomitant benzodiazepines or the medical visits made. Another limitation is the heterogeneity associated to the intervention of the 90 psychiatrists-investigators, although an attempt was made to minimize this aspect through a previous meeting on the standardization of the instruments to be used by all the professionals who participated.

The parameters regarding the social demographic features of the samples studied show a great agreement with the values accepted in the epidemiology of depression<sup>1-6</sup>. Furthermore, the parallelism regarding recent studies in depressive populations of our setting has been verified. This provides greater force to the findings described and support the representativity of the patients included.

Analyses of these study results showed the following conclusions:

- Mirtazapine is effective in the treatment of depression and in a precocious way. Statistically significant improvement of the depression and of the associated somatic symptoms is observed already from the first control done at 15 days of treatment. According to the results obtained, mirtazapine was effective at a mean dose of 30 mg/day used for 12 weeks. The intensity of the depression had already decreased in the first control, with significant decrease in the mean value on the HAMD-17 scale from 23.27 to 16.81, with a final mean value of 6.75. The decrease on the score of the Hamilton scale in the first control regard-

Adverse events	No. pat	%
Somnolence/sedation	50	7.03
Increase in appetite and weight	20	2.81
Headache	10	1.40
Dizziness/instability	9	1.26
Gastrointestinal disease	6	0.84
Circulatory alterations	6	0.84
Anxiety	5	0.70
Pains	3	0.42
Asthenia	3	0.42
Insomnia	2	0.28
Skin alterations	1	0.14
Others	12	1.68

ing debt obtained in the baseline control was 27.77% ( $p < 0.0001$ ). The decrease in the score in the second control was 52.64% ( $p < 0.0001$ ) and 70.25% in the final control ( $p < 0.0001$ ). Another way of evaluating efficacy is by means of the rates of response to treatment, taking decrease of the score on the Hamilton scale during the follow-up in more than 50% in relationship to the baseline value as criterion of good response. A statistically significant improvement was observed in all the items of the scale, that was even more important in the items of depressive mood, anxiety and insomnia.

- Mirtazapine is effective in the treatment of somatic symptoms of depression early: intensity of the somatic symptoms decreased in the first control, the number of somatic symptoms measured with the SPPI significantly decreasing from 7.68 to 5.39, with a mean final value of 2.28. The SPPI score in the first control had already decreased by 29.85% ( $p < 0.0001$ ) in relationship to the score obtained in the baseline control. In the second control, decrease in the score was 52.84% ( $p < 0.0001$ ) and of 70.25% in the final control ( $p < 0.0001$ ).
- Mirtazapine is as effective in the treatment of the different groups of somatic symptoms that appear in depression. We found a significant improvement of all the groups of somatic symptoms (pain, digestive symptoms, cardiovascular discomfort, etc.) from the first control that significantly continued in the remaining controls.
- In regards to the attribution of the somatic symptoms, those patients in the sample who thought that the cause of these symptoms was psychological went from 41.37% in the baseline visit to 63.94% 90 days after treatment with mirtazapine, a significant increase. Mirtazapine could be capable of modifying the attribution of the somatic symptoms in somatizers and transform these patients into psychologizers, who are easier to treat. However, given that this is not a controlled study, this fact cannot be confirmed because other factors, such as the concomitant use of other medications or visit to the medical office on several occasions may have an effect. This is the first international subject that suggests, with all the limitations explained, that the somatic attribution of the somatizers could be modified exclusively by drug treatment without needing to use the reattribution psychological techniques of Goldberg.
- Mirtazapine decreases the concomitant use of benzodiazepines. It has been observed that during the study concomitant treatment of anxiolytics or hypnotics decreased, this suggesting the lack of need to associate them to mirtazapine. The improvement of the depression and of the somatic symptoms during the study was obtained almost without needing to associate benzodiazepines concomitantly. Approximately half of the sample (48.52%) took benzodiazepines at the

beginning of the study while after 90 days of treatment with mirtazapine, only 6.71% of the patients required the association of benzodiazepines.

- Mirtazapine has a good safety profile. Tolerability follows a coherent pattern to that expected according to the data of the previous studies with mirtazapine, no other side effects that were not previously described appearing significantly. The incidence of adverse effects was less than that mentioned in other studies since only 13.36% of the patients had adverse events that were spontaneously reported. This fact may be related with the study duration that was limited to 12 weeks. The profile of the side effects of mirtazapine coincides, although in lesser proportion, with that of the previous bibliography, with appearance of somnolence or sedation (7.03% of the population studied), increase of appetite or weight (2.81%) and headache (1.40%). Of all those who dropped out of the study, only 4% were due to adverse events. However, it must be kept in mind that the evaluation of the side effects was not the primary objective of the study. Thus, specific scales were not administered, or in the case of weight gain, the patients were not weighed, exclusively trusting what they reported. For these reasons, it is very likely that the percentage of side effects is underestimated.

The MEDAS study, with the obvious limitations of open label studies but also with the advantages of demonstrating what occurs in the clinical practice, shows that in a sample which is representative because of its size and characteristics of the general population of depressive patients with associated somatic symptoms in our country, mirtazapine already significantly acts by reducing the symptoms from the first control. The improvement of the symptoms is already shown both on the Hamilton scale and on SPPI, with statistically significant and clinically relevant differences in all the controls from the first control.

## REFERENCES

1. Üstün TB Sartorius N. Public health aspects of anxiety and depressive disorders. *Int Clin Psychopharmacol* 1993;8 (Suppl. 1): 15-20.
2. Angst J. Epidemiology of depression. *Psychopharmacol* 1992; 106:571-4.
3. Kind P, Sorenson J. The cost of depression. *J Clin Psychiatry* 1993;54:191-5.
4. Hamilton M. Frequency of symptoms in melancholia (depressive illness). *Br J Psychiatry* 1989;154:201-6.
5. Katon W, Russo J. Somatic symptoms and depression. *J Fam Practice* 1989;29:65-9.
6. Ebert D, Martus P. Somatization as a core symptom of melancholic type depression. Evidence from a cross-cultural study. *J Affect Disord* 1994;32:253-6.
7. Katon W. Panic disorder and somatization. Review of 55 cases. *Am J Med* 1984;77:101-6.

8. Gureje O, Simón GE, Üstun TB, Goldberg DP. Somatization in cross-cultural perspective: a World Health Organization study in primary care. *Am J Psychiatry* 1997;154:989-95.
9. Simon G, Gater R, Kisely S, Piccinelli M. Somatic symptoms of distress: an international primary care study. *Psychom Med* 1996;58:481-8.
10. Lobo A, García-Campayo J, Campos R, Marcos G, Pérez-Echeverría MJ, Lobo A, et al. Somatisation in primary care in Spain. I. Estimates of prevalence and clinical characteristics. *Br J Psychiatry* 1996;168:344-8.
11. Frank E, Kupfer DY, Thase M. New psychopharmacologic and psychotherapeutic strategies for long-term treatment of mood disorders. En: Costa e Silva YA, Nadelson CC, editores. *International Review of Psychiatry*, vol. I. American Psychiatric Press (in conjunction with Ninth World Congress of Psychiatry). Washington DC, 1993.
12. Baldessarini RY. Current status of antidepressants: clinical pharmacology and therapy. *J Clin Psychiatry* 1989;50:117-26.
13. Van Praag HM, Asnis GM, Kahn RS. Monoamines and abnormal behaviour: a multiaminergic perspective. *Br J Psychiatry* 1990; 157:723-34.
14. De Boer T, Ruigt GSF and Berendsen HHG. The  $\alpha_2$ -selective adrenoceptor antagonist Org 3770 (mirtazapine, Remeron) enhances noradrenergic and serotonergic transmission. *Hum Psychopharmacol* 1995;10(Suppl. 2):S107-19.
15. Kasper S. Clinical efficacy of mirtazapine: a review of meta-analysis of pooled data. *Int Clin Psychopharmacol* 1995;10 (Suppl. 4):25-37.
16. Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain* 1992;49:205-20.
17. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278-96.
18. Lobo A, Campos R, Pérez-Echevarría MJ, Izuzquiza J, García-Campayo J, Saz P, et al. A new interview for the multiaxial assessment of psychiatric morbidity in medical settings. *Psycholog Med* 1993;23:505-10.
19. García-Campayo J, Campos R, Marcos G, Pérez-Echeverría MJ, Lobo A, GMPPZ. Somatisation in primary care in Spain. II. Differences between somatisers and psychologisers. *Br J Psychiatry* 1996;168:348-53.